By the Restriction Response filed December 19, 1990, Applicants elected the Group I invention (Claims 1-7) for further prosecution in this application. By the present Amendment, Applicants have cancelled Claims 8 and 9, drawn to the non-elected invention, without prejudice to the filing of one or more divisional applications directed to the subject matter thereof.

This invention relates to a physiologically active polypeptide, a DNA encoding the polypeptide, and a pharmaceutical composition for treating and curing circulation diseases comprising the polypeptide as an effective ingredient.

Structures of new polypeptides secreted by human or rat atria and having natriuretic activity have successively been determined and reported in the years 1983-1984 [*Biochem. Biophys. Res. Commun.* 117, *859 (1983); Biochem. Biophys. Res. Commun.* 118, *131-139 (1984)*]. These polypeptides were named atrial natriuretic peptides (hereinafter referred to as "ANP"). Since they have strong natriuretic activity as well as relaxing activity of vessel and smooth muscle, they are attracting much attention as a new peptide medicine for circulatory disease.

In 1988, a new peptide having diuretic activity was isolated in a purified form from porcine brain. Its structure was determined and the peptide was named "porcine brain natriuretic peptide" (hereinafter referred to as porcine BNP

or pBNP) [*Nature, 332, No. 6159, 7881 (1988); Biochem. Biophys. Res. Commun. 155, 726-732 (1988)*]. Pharmaceutical activities of pBNP resemble those of ANP, and include diuretic activity, natriuretic activity, vasodepressor activity, chicken rectum relaxation activity, and the like. The specific activities of pBNP also resemble those of ANP, except that the rectum relaxation activity of pBNP is 3 to 4 times higher than that of ANP. This is the reason that pBNP is expected to be a new medicine for circulatory disease and that studies involving DNA of porcine BNP are being undertaken. Cloning of cDNA possessing a base sequence encoding porcine BNP and its precursor has been reported [*Biochem. Biophys. Res. Commun. 157 (1), 410-416 (1988)*].

Development of brain natriuretic peptide derived from human being (hereinafter referred to as human BNP or hBNP) has been desired as a therapeutic agent for human circulatory diseases. Such a peptide, however, has not been heretofore found.

In view of this situation, the present inventors have conducted extensive studies to obtain human BNP, and have been successful in cloning cDNA encoding human BNP by screening a cDNA library.

Furthermore, the present inventors have synthesized various human BNPs based on the amino acid sequence deduced from the cDNA base sequence and have studied their pharmacological activities. As a result, the inventors have

found that these BNPs had excellent smooth muscle relaxation and natriuretic activities.

Claims 1-7 have been rejected under 35 U.S.C. 103 as being unpatentable over Sudoh et al in view of Suggs et al. This ground for rejection is respectfully traversed.

As noted by the Examiner, Sudoh et al disclose the isolation of porcine brain natriuretic peptide (pBNP) and the amino acid sequencing of the peptide.

Suggs et al disclose the preparation of oligonucleotide probes for the isolation of genes from cDNA libraries.

Based on these disclosures, the Examiner concludes that it would have been obvious to construct oligonucleotide probes from the pBNP amino acid sequence of Sudoh et al to screen a human cDNA library for the human BNP gene.

It is respectfully submitted that this conclusion reads more into the references than is disclosed therein. In this regard, Suggs et al specifically state, page 6613, left-hand column:

> "Our general approach is to chemically synthesize a mixture of oligonucleotide that represent all possible codon combinations for a small portion of the amino acid sequence of a given protein. Within this mixture must be one sequence complementary to the DNA coding for that part of the protein. This complementary oligonucleotide will form a perfectly base paired duplex with the DNA from the coding region for the protein whereas the other oligonucleotides in the mixture will form mismatched duplexes. Under stringent hybridization conditions only the perfectly matched duplex will form, allowing the use of the mixture of oligonucleotides as a specific hybridization probe. Mixed sequence oligonucleotide probes should allow isolation of

> cloned cDNA sequences for <u>any protein for which the amino acid sequence is known</u>." (Emphasis supplied.)

Moreover, as further noted by <u>Suggs et al</u>, at page 6614, right-hand column:

> "Our general approach for the isolation of cloned DNA sequences specific for β_2m involved synthesis of a set of oligodeoxyribonucleotides complementary to all the possible coding sequences for a small portion of the protein. <u>In designing the probe sequences, we chose two regions of the protein for which there are relatively few potential coding sequences</u>. (Emphasis supplied.)

As may be readily ascertained from the above, <u>Suggs et al</u> requires a knowledge of the amino acid sequence of the protein. In this regard, Applicants are the first to isolate human brain natriuretic peptide (hBNP). Thus, prior to Applicants work there was no hBNP for use in the design of a probe. Moreover, while a high degree of homology between pBNP and α-hANP has been shown by <u>Sudoh et al</u>, this would not provide basis for the preparation of a probe for hBNP since (1) there is no way of knowing which sequences of the pBNP should be selected for probe construction and (2) it would appear that the probe would be more likely to find α-hANP rather than the unknown hBNP.

As such, this ground for rejection is deemed to be in error and should be withdrawn.

Claim 1 has been rejected under 35 U.S.C. 112 (first paragraph and second paragraph). Cancellation of Claim 1 is deemed to have been rendered this ground for rejection moot.

Accordingly, this application is now deemed to be in condition for allowance and early notice to that effect is earnestly solicited.

Respectfully submitted,

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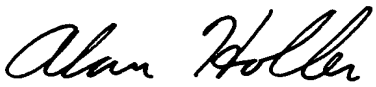

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